Remarks

This amendment amends the specification and adds new claims 48-67. No new matter has been added.

Applicants' Attorney hereby states that the amendments in the specification, the insertion of Figure 1 and Figure 2, and the changes made in the Sequence Listing do not include new matter. The Amendment corrects a formal matter without changing the scope of the claims.

The specification has been amended by inserting Formal Drawings, Figure 1 and Figure 2, in accordance with M.P.E.P. § 210.06(c), that were inadvertently omitted from the application parts submitted on November 28, 2000. This insertion does not add new matter to the specification since Figure 1 and Figure 2 were originally filed in a parent application Serial No. 09/220,077 incorporated by reference in the present application.

The specification has been amended by inserting SEQ ID NO:4 next to the amino acid sequence on page 12, line 32, of the specification that had inadvertently been unidentified. The Sequence Listing has been amended to insert the sequence for SEQ ID NO:4 at the end of the original Sequence Listing of April 22, 1999. Support for this amendment is found at page 12, line 32, of the original specification. Further, field <160> has been amended to recite the correct number of the sequences. The Sequence Listing has also been amended by correcting the numbering of the amino acid residues in SEQ ID NO:1 and SEQ ID NO:2 to start from the glycine residue instead of the methionine residue. Support for this amendment can be found in Figure 1 originally filed in the parent application Serial No. 09/220,077. Furthermore, field <120> has been amended to recite the current title. Applicants' Attorney has amended the

specification only to direct the entry of this Substitute Sequence Listing at the end of the application and to provide the SEQ ID NO next to the specific sequence.

In accordance with 37 C.F.R. § 1.821(g), this submission includes no new matter.

In accordance with 37 C.F.R. § 1.825(b), the paper copy of the Substitute Sequence Listing and the computer-readable copy of the Substitute Sequence Listing submitted herewith are the same.

Support for new claims 48- 67 can be found in the specification and claims as originally filed. New claims 48 and 49 have support at page 8, lines 8-12, of the specification. New claims 50-67 are supported throughout the specification as filed, *inter alia*, at page 11, lines 11-20, at page 13, lines 10-15, at page 14, lines 16-20, at page 15, lines 11-15 and 20-25, at page 24, lines 5-6, and at page 25, lines 4-26.

Upon entry of the foregoing amendment, claims 1-8, 17-38, 40, and 48-67 are pending in the application, with claims 1, 50, and 59 being the independent claim. As such, no new matter has been introduced into the captioned application.

I Priority

The Examiner has requested the application be amended by including the current status of all nonprovisional parent applications referenced. Applicants have amended the first paragraph of the specification by inserting the current status of the parent application No. 09/220,077.

II Description of the Invention

The present invention is directed to muteins of human basic fibroblast growth factor (bFGF), or biologically active peptides thereof, that have improved mitogenic agonist activity. Applicants have found that this improved activity over wild-type bFGF can be achieved by mutating at least one of glutamate at position 89, aspartate at position 101 and leucine at position 137, wherein the numbering of amino acids is based on SEQ ID NO:1. Accordingly, the object of the invention is to provide muteins of human basic fibroblast growth factor, or biologically active peptides thereof, having improved mitogenic agonist activity wherein one or more of the amino acids glutamate 89, aspartate 101 or leucine 137 are substituted with a neutral and/or a hydrophobic amino acid.

III Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-8, 17-38, and 40 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the substitution of position 89 with either alanine or tyrosine and the substitution of either positions 101 or 137 with alanine, allegedly does not reasonably provide enablement for substitution of those positions with any neutral amino acid or hydrophobic amino acid. The Examiner further alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The enablement requirement of § 112, first paragraph, ensures that one skilled in the art will be able to make and use the invention. Further, the test of enablement is not whether any

experimentation is necessary, but whether, if experimentation is necessary, it is undue. M.P.E.P. § 2164.01.

The reasons behind the Examiner's rejection are as follows:

> [A]lanine in the only amino acid which has been substituted as [*sic*] all three positions and tyrosine has only been substituted at position 89 and one of ordinary skill in the art would not find these substitutions predictive of all amino acids which are encompassed by the claim limitations of neutral or hydrophobic amino acids.

At page 3, lines 8-12, of the Office Action.

> [O]ne cannot predict from the substitution of alanine at these positions what biological property will be possessed by the other substitutions.

At page 4, lines 12-13, of the Office Action.

> The instant claims are not limited to naturally occurring compounds and the instant specification does not provide a description of a repeatable process of producing a protein which has the same biological activity as the alanine substitutions.

At page 5, lines 9-12, of the Office Action.

> To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work described in the instant application, but a substantial inventive contribution on the part of a practitioner which would involve the determination of which substitutions and combinations of substitutions would result in the biological activity of superagonist. The decisions of *In re Fisher*, Amgen Inc. V. Chugai, and *In re Wands* have been relied upon the instant rejection and by the court in a recent CAFC decision, Genentech, Inc. V. Novo Nordisk . . .

At page 5, lines 9-16, of the Office Action.

According to the Examiner, experimentation would be undue and the claims are, therefore, not enabled by the specification because

> each embodiment would need to be made and tested because there is not a reasonable expectation that any one embodiment would possess the required activity of the claims. The guidance in the specification is not sufficient to direct the skilled artisan to those embodiments which would more likely than not possess the required activity, the number of embodiments encompassed is quite large, predictability is lacking, there is a lack of guidance in the prior art, and the amount of experimentation is great as every mutant would need to be made and tested for activity.

At page 9, lines 5-11, of the Office Action.

Regarding the Declaration Under 37 C.F.R. § 1.132 by Barry Springer filed November 28, 2000 ("Springer Decl."), the Examiner argues that it is insufficient to overcome the instant rejection because, according to the Examiner, it fails to establish that substitution with either a neutral or hydrophobic amino acid would provide for the biological effect that was seen with a substitution with alanine.

To support the rejection, the Examiner cites Robson *et al.* (*Introduction to Proteins and Protein Engineering*, p. 41 (1986)), Kopchick *et al.* (U.S. Pat. No. 5,350,836), and Cunningham *et al.* (*Science 247*:1306-1310 (1990)). Robson *et al.* state that "the changing of one amino acid in a sequence gives, by definition a new protein" and "it cannot be assumed a priori that changing even one amino acid will not significantly, perhaps even drastically, alter the properties of a protein". According to the Examiner, Kopchick *et al.* can be used as evidence that not all amino acids can be substituted one for another and preserve the function of the protein. The Examiner cites Cunningham *et al.* to show that substitution of neutral amino acids with alanine does not necessarily preserve protein function. Applicants respectfully disagree.

It is respectfully submitted that the enablement of claims 1-8, 17-38, and 40 is supported by the specification as filed and publications available at the time the above-captioned application was filed for at least the following reasons.

Contrary to Robson *et al.*, there is ample evidence in the literature that usually small, minor local changes in a protein do *not* change the activity or the overall structure of the protein. For example, Watson *et al.* describe that single amino acid substitutions usually do not alter enzyme activity (See ¶8, Springer Decl.). This has also been acknowledged at the U.S. Patent and Trademark Office, Board of Appeals and Interferences. See *Ex parte Maizel*, 27 U.S.P.Q. 2d. 1662 (B.P.A.I. 1993). Furthermore, Bowie *et al.* has examined amino acid substitutions within a protein and the likelihood that such mutations will affect biological activity. The authors reported that proteins are surprisingly tolerant of amino acid substitutions, and that the choice of substitution at a given amino acid residue depends, in part, on the location of the residue within the protein's three dimensional structure (See ¶8, Springer Decl.).

The Examiner is correct that Kopchick *et al.* describe that substitution of any amino acid for the glycine at position 119 in bovine growth hormone results in a growth hormone antagonist. Indeed, Kopchick *et al.* found that the replacement of the glycine at position 119 is essential in order to achieve the antagonistic activity, i.e., they found the right amino acid position for this particular activity. However, it should be noted that the glycine 119 residue of Kochick *et al.* is a buried position in bovine growth hormone (See FIG. 3 of Kopchick *et al.*). Therefore, Applicants respectfully submit that at best Kopchick *et al.* can be used as evidence that the substitutions at the buried amino acid position glycine 119 are likely to destroy the structure of the protein thereby modifying the function of the protein to an antagonist.

Cunningham *et al.* does not remedy the deficiences of Kopchick *et al.* Cunningham *et al.*, Fig. 1 and Table 1, indeed describe that most of the mutants show no essential change in the binding affinity or they show a lower binding affinity compared to that of the wild-type human growth hormone. However, it is respectfully submitted that the lack of success of Cunningham

et al. to find the amino acid positions which should be mutated to alanine in order to achieve a human growth hormone with higher binding affinity should not be held against the present invention. In fact, Cunningham *et al.* can be used as evidence that when the mutagenesis does not change the protein structure, the function of the protein is conserved (See ¶8, Springer Decl.).

In the present application, the invention lies in the discovery that the replacement of one or more of the amino acids glutamate at position 89, aspartate at position 101 or leucine at position 137 with a neutral and/or hydrophobic amino acid provides a mutein with improved mitogenic agonist activity. These positions, glutamate 89, aspartate 101 and leucine 137, are on the surface of the protein, not buried as is glycine 119 in the Kopchick *et al.* reference (See ¶8, Springer Decl.). Surface amino acid positions are more tolerant of substitution than buried amino acid positions. It is not surprising that substitution at a buried position disrupts structure and renders the function unpredictable. Surface substitution is more conservative of structure and, thus, of function.

Applicants have in fact shown in the instant specification that substitutions at any of these surface amino acid positions with alanine or at position 89 with tyrosine do not destroy the protein structure but protect it, because the protein function is preserved. Hence, proteins with mitogenic agonist function are provided. Moreover, Applicants have shown that the substitutions not only provide a conserved mitogenic agonist function, but an improved mitogenic agonist function. Alanine and tyrosine are predictive of other neutral and/or hydrophobic amino acids because one of ordinary skill in the art can reasonably extrapolate from the substitutions with alanine and tyrosine to substitutions with other neutral and/or hydrophobic amino acids. This is evidenced by Dr. Springer in his Declaration.

Dr. Springer's Declaration provides evidence that 1) glutamate at position 89, aspartate at position 101 or leucine at position 137 were known in the art to be located on the surface of the human bFGF (See ¶6, Springer Decl.), and that 2) neutral and/or hydrophobic substitutions on the surface of the protein are accommodated and do not destroy the structure of the protein (See ¶5, Springer Decl.), and, therefore, 3) the function of the protein is not changed. Hence, it would have been reasonably expected at the time the application was filed that substitutions at glutamate 89, aspartate 101, and leucine 137 with a neutral and/or hydrophobic amino acids protect the structure of human bFGF and, thus, provide a protein with mitogenic agonist, or even improved mitogenic agonist, function. Furthermore, Dr. Springer's Declaration provides evidence that the art was predictable at the time of the application was filed. The state of the art was advanced and the level of ordinary skill was very high at the time the application was filed. Therefore, only routine experimentation would have been required for the preparation and screening of muteins at the time the application was filed.

Thus, contrary to the Examiner's arguments, in view of the specification and the evidence of record, it is respectfully submitted that a person skilled in the at the time the application was filed would have been able to make and use the present invention without undue experimentation commensurate in scope with the claims.

Factors to be considered in determining whether pending claims would require undue experimentation have been articulated by the Court of Appeals for the Federal Circuit in *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). They include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the

predictability or unpredictability of the art, and (8) the breadth of the claims.

Considering the above factors, it is respectfully submitted that Applicants' invention does not reasonably require undue experimentation.

Factor No. 1, quantity of experimentation. The Examiner has not sought to quantify the amount of experimentation, but rather notes in a conclusory fashion that the amount of experimentation is undue, as every mutant would need to be made and tested for activity. However, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). As discussed by Dr. Springer, only routine experimentation would have been required to generate muteins of bFGF according to the invention having improved mitogenic agonist activity (See ¶13, Springer Decl.). In addition, the specification provides a reasonable amount of guidance (See *Factor No. 2*). There was lengthy experimentation and trial and error in *Wands*, yet the court held that it was routine. The same is true here.

Factor No. 2, the amount of direction or guidance presented. The Examiner alleges that guidance in the specification is not sufficient to direct the skilled artisan to those embodiments which would more likely than not possess the required activity. According to the Examiner, this is because the claims are not limited to naturally occurring compounds and the specification does not provide a description of a repeatable process of producing a protein which has the same biological activity as the alanine substitutions.

It is respectfully submitted that non-naturally occurring analogs of neutral and hydrophobic amino acids as defined at page 8, lines 8-12, of the specification can be prepared

by methods known in the art, or they are commercially available, e.g., by Peptech Corporation. Further, the muteins of human bFGF, or biologically active peptides thereof, according to the present invention can be prepared by simple mutagenesis. At the time the above-captioned application was filed, plenty of guidance on protein mutagenesis was available to protein biochemists of ordinary skill. For example, methods described at page 9, lines 11-16, and at page 10, lines 3-11, of the specification and in Example 1 can be used. This is supported by Dr. Springer's Declaration (See ¶11, Springer Decl.). As supported by case law, Applicants need not supply information that is well known in the art. See *In re Howarth*, 654 F.2d 103, 105-6, 210 U.S.P.Q. 689, 692 (C.C.P.A. 1981); *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d at 1366, 42 U.S.P.Q.2d at 1005; and *In re Brebner*, 455 F.2d 1402, 173 U.S.P.Q. 169 (C.C.P.A. 1972). Moreover, one of ordinary skill in the art is deemed to know not only what is considered well known in the art but also where to search for any needed starting materials. See *In re Howarth*, 654 F.2d 103, 105-6, 210 U.S.P.Q. 689, 692 (C.C.P.A. 1981).

Further, mitogenic agonist activity of the bFGF mutant proteins according to the invention can be determined by simply comparing mutein and wild-type bFGF stimulation of fibroblast growth. The method of screening is described in detail in Example 3 of the specification. A person of ordinary skill at the time the above-captioned application was filed would have been able without undue experimentation to follow the guidance of the specification and determine whether a mutein has improved mitogenic agonist activity. This is also supported by Dr. Springer's Declaration (See ¶12, Springer Decl.).

Thus, contrary to the Examiner's arguments, the instant specification provides a description of a repeatable process for preparing the muteins of the present invention in Example 1, and a repeatable process for testing their mitogenic activity in Example 3. Example 1

describes a repeatable process for substitution with both a neutral amino acid, alanine, and a hydrophobic amino acid, tyrosine. The process of testing described in Example 3 was used in three different cell lines, i.e., Swiss 3T3, NIH 3T3, and Balb/c 3T3, and the results remained consistent for all three cell lines tested. Moreover, Table 1 of the specification shows by the number of experiments conducted for each tested mutein that the test procedure is repeatable.

According to M.P.E.P. § 2164.01(b),

> [a]s long as the specification discloses at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. . . . Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112.

Applicants respectfully submit that the instant specification has met this burden.

In view of the above, the Examiner has not provided any factual basis on which it can be concluded that one skilled in the art would not be able to prepare muteins of human bFGF according to the invention having improved mitogenic agonist activity other than those expressly exemplified.

Factor No. 3, the presence or absence of working examples. The specification provides working examples on the preparation of 6 muteins of the present invention and the test for screening the mitogenic agonist activity of the muteins (see *Factor No. 2*).

A specification need not contain a single working example. See *In re Borkowski*, 164 U.S.P.Q. 642 (C.C.P.A. 1970). Further, representative examples together with a statement applicable to the genus as a whole will be sufficient if one skilled in the art would expect the claimed genus could be used in that manner without undue experimentation. See M.P.E.P. § 2164.02. Therefore, it is respectfully submitted that the Examiner has not provided adequate

reasons to establish that a person skilled in the art could not make and use muteins of the present invention other than the ones expressly exemplified without undue experimentation.

Factor No. 4, the nature of the invention. The Examiner has not determined the nature of the invention, i.e., the subject matter to which the claimed subject matter pertains, but states as follows:

> The instant specification is directed to mutants of human basic fibroblast growth factor wherein the amino acids at positions 89, 101, and/or 137 are substituted with either a neutral or hydrophobic amino acid.

At page 3, lines 3-5, of the Office Action.

Factor No. 5, the state of the art. The Examiner has not addressed this issue. It is respectfully submitted the state or the art was advanced at the time the application was filed. Protein mutagenesis has been known in the art for at least 15 years, and thousands of articles have been published on targeted mutagenesis.

Factor No. 6, the relative skill of those in the art. The Examiner has not addressed this issue. Given the state of the art and the source of publications and patents in the art, it is clear that the skill level in the art of muteins of human bFGF and their use for, e.g., stimulating cell division is high, typically that of a Ph.D. level worker.

Factor No. 7, the predictability or unpredictability of the art. The Examiner asserts that predictability is lacking. Specifically, as discussed above, the Examiner asserts that one of ordinary skill in the art would not conclude that the substitution of amino acid positions 89, 101 and 137 with alanine is predictive and exemplary of the other amino acids which are encompassed by the claims or the biological property. Applicants respectfully disagree and submit that the art was predictable at the time the application was filed.

To support her allegations, the Examiner cites Robson *et al.*, Kopchick *et al.*, and Cunningham *et al.* All these references have already been discussed above. Kopchick *et al.* teach that substitutions at the buried amino positions are very likely to disrupt the structure of the protein and thereby change the function of the protein. Cunningham *et al.* failed to find amino acid positions in a human growth hormone which mutated would have provided higher binding affinities, and is evidence that if the protein structure is not changed by mutagenesis, the function of the protein is conserved. Finally, Robson *et al.* is contrary to well-acknowledged principles on the effects of amino acid substitutions on the structure and function of proteins, and even caselaw. See Watson *et al.* (Appendix 6 of Springer Decl.) and Bowie *et al.* (Appendix 5 of Springer Decl.). See also *Ex parte Maizel*, 27 U.S.P.Q. 2d. 1662 (B.P.A.I. 1993). Thus, the cited references do not provide any reasonable basis for the Examiner's allegation on unpredictability. To the contrary, the cited references along with Watson *et al.*, Bowie *et al.* and the instant specification, support the predictability of this area of the art.

As discussed above, Applicants have shown in the specification that the substitutions at one or more of the surface positions glutamate 89, aspartate 101 and leucine 137 with another neutral amino acid and/or a hydrophobic amino acid do not disrupt the structure of human bFGF. The conservation of the function of the mutein, i.e., the mitogenic agonist activity, is the proof of protected protein structure. Therefore, it can be reasonably expected that the substitution of alanine at one or more of the positions glutamate 89, aspartate 101 and leucine 137 with another neutral amino acid and/or a hydrophobic amino acid will provide the biological effect seen by alanine substitutions at those positions (See ¶8, Springer Decl.). Furthermore, protein mutagenesis and methods of screening mitogenic agonist activity of proteins are well known in

the art. Thus, only routine experimentation would have been required to prepare muteins of human bFGF having improved mitogenic agonist activity.

Contrary to the Examiner's arguments, these conclusion are, in fact, supported by evidence. Dr. Springer's Declaration is that evidence. Applicants respectfully submit that a "declaration or affidavit is, itself, evidence that must be considered." See M.P.E.P. § 2164.05. Furthermore, Dr. Springer's Declaration cites several references, i.e., provides factual evidence, to support the conclusions.

In view of the above, the Examiner has not provided any factual basis on which it can be concluded that the art is so unpredictable that one skilled in the art would not be able to prepare muteins of human bFGF according to the invention having improved mitogenic agonist activity.

Factor No. 8, the breadth of the claims. The Examiner alleges that the instant application does not support the breadth of the claims and cites the decisions of *In re Fisher*, *Amgen Inc. v. Chugai Pharmaceutical Co.*, *In re Wands*, and *Genentech, Inc. v. Novo Nordisk* for support.

Applicants respectfully disagree. The claims are not unduly broad. They are in fact limited to conservative changes at only three surface positions. The claims are not drawn to all substitutions at three surface positions, and they are not drawn to conservative substitutions at all positions.

None of *In re Fisher*, *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* and *Genentech Inc. v. Novo Nordisk A/S* is applicable. The issue in *In re Fisher* was whether an open-ended recitation in a claim rendered the claim too broad, and the present claims do not include any open-ended recitation. *Amgen* relates to the breadth of a single means claim, and the present

claims do not include any single means claim. *Genentech* does not deal with the breadth of the claims.

Contrary to the Examiner's arguments, it is respectfully submitted that *In re Wands* applies in favor of the present case. The facts of *In re Wands* are similar to those of the present application and, thus, support Applicants position. In *In re Wands*, the issue was whether the specification enabled one skilled in the art to make the monoclonal antibodies that are needed to practice the invention. The procedure for preparing monoclonal antibodies against a particular antigen involved, *inter alia*, screening of hybridomas to determine which ones secrete antibody with desired effects. Wands carried out the entire procedure three times, and was successful each time in making at least one antibody that satisfied all the claim limitations. The fact that a number of hybridomas were never screened was irrelevant. Similarly, in the present case, the inventors carried out the procedure for preparing a mutein according to the present invention 6 times and each time they were successful in making a mutein that satisfied all the claim limitations. The court concluded in *In re Wands* that the claims were enabled because the disclosure provided considerable direction and guidance on how to practice their invention and presented working examples, there was a high level of skill in the art at the time the application was filed, and all the methods needed to practice the invention were well known. See *In re Wands*, 8 U.S.P.Q.2d at 1406 (Fed. Cir. 1988). In view of the above, the conclusion of *In re Wands* should also be made in the present case.

Dr. Springer's credentials have not been criticized by the Examiner. Hence, the objective truth of Dr. Springer's Declaration must be accepted in the absence of good reason to the contrary. In fact, the court has cautioned personnel in the PTO against substituting their opinions for those of experts in the art. See *In re Zeidler*, 215 U.S.P.Q. 490 (C.C.P.A. 1982), *In re*

Piasecki and Meyers, 745 F.2d 1468 (Fed. Cir. 1984), *In re Alton*, 37 U.S.P.Q.2d 1578 (Fed. Cir. 1996), and *Ex parte John E. Webster*, Appeal No. 91-3410 (B.P.A.I. 1992) (unpublished). Furthermore, all the evidence related to each of the above factors, and any conclusion of enablement must be based on the evidence as a whole. See M.P.E.P. § 2164.01(a). Therefore, it is respectfully submitted that the Examiner's rejection is not supported. See *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

In view of the above, reconsideration and withdrawal of the rejection of claims 1-8, 17-38, and 40 under 35 U.S.C. § 112, first paragraph, are respectfully requested.

IV Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1-8, 17-38, and 40 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner alleges that the claims are indefinite for the recitation of mutein because naturally occurring amino acids are encompassed by the claims. The Examiner's arguments are as follows:

> The instant claims encompass the substitution of position 137 with a hydrophobic amino acid, which includes the naturally occurring amino acid leucine at this position. It is not clear how the substitution of leucine at position 137 with leucine would provide for a mutein, wherein the specification describes a mutein as having an altered property, structural or functional.

Applicants respectfully disagree. It would be clear for a person skilled in the art wishing to substitute leucine at position 137 with a hydrophobic amino acid in order to get a mutein

having altered property, not to select leucine for the substitution but another hydrophobic amino acid. The recitation of the word "mutein" in claim 1 makes it clear that naturally occurring amino acids are not intended to be encompassed by the claims.

Further, the Examiner alleges that the recitation "comprising the substitution of a neutral and/or hydrophobic amino acid for one or more of the following" is confusing because, according to the Examiner, it seems to imply that two amino acids could replace one of the recited amino acids. Applicants respectfully disagree. It is clear from the specification at page 8, lines 13-18, that claims 1 and 23 encompass replacement of one amino acid with one amino acid.

In view of the above, reconsideration and withdrawal of the rejection of claims 1-8, 17-38, and 40 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

V Double Patenting

The Examiner has rejected claims 1-8, 17-38, and 40 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-9 of U.S. Patent No. 6,274,712 B1. Applicants respectfully traverse this rejection.

In order to advance the prosecution of the present application, Applicants hereby submit Terminal Disclaimer to Obviate a Double Patenting Rejection Under 37 C.F.R. § 1.321(c).

In view of the above, reconsideration and withdrawal of the rejection of claims 1-8, 17-38, and 40 under the judicially created doctrine of obviousness-type double patenting are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

John M. Covert
Reg. N. 31,759

for Jorge A. Goldstein
Attorney for Applicants
Registration No. 29,021

Date: Aug. 21, 2002

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

In the Specification:

The first paragraph has been amended as follows:

This is a continuation of U.S. Patent Application Serial No. 09/220,077, filed December 23, 1998, now U.S. Patent No. 6,274,712 B1, which claims the benefit, under 35 U.S.C. § 119(e), of the earlier filing date of U.S. provisional application, Appl. No. 60/068,667, filed on December 23, 1997. The entirety of each of these applications is incorporated by reference herein.

The paragraph beginning on page 12, line 29, has been amended as follows:

The mutein of the present invention may also have the coding sequence fused in frame to a marker sequence which allows for purification of the mutein of the present invention. The marker sequence may be a hexa-histidine tag or the T7 peptide (amino acid sequence: Met Ala Ser Met Thr Gly Gly Gln Gln Met Gly (SEQ ID NO:4)) supplied by a vector to provide for purification of the polypeptide fused to the marker in the case of a bacterial host, or, for example, the marker sequence may be a hemagglutinin (HA) tag when a mammalian host, e.g. COS-7 cells, is used. The HA tag corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson, I., *et al.*, *Cell 37*:767 (1984)). Other marker sequences well known to those skilled in the art may be used for similar purposes.

In the Claims:

New claims 48-67 have been added.